Ophthalmologica

Original Paper

Ophthalmologica 2015;234:40–54
DOI: 10.1159/000381865

Received: December 23, 2014
Accepted after revision: March 3, 2015
Published online: June 18, 2015

Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial

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Key Words
Age-related macular degeneration · Choroidal neovascularization · Corticosteroid · Dexamethasone · Intravitreal implant · Ranibizumab

Abstract
Purpose: To evaluate the efficacy and safety of dexamethasone intravitreal implant 0.7 mg (DEX) as adjunctive therapy to ranibizumab in neovascular age-related macular degeneration (nvAMD). ***Procedures:*** This was a 6-month, single-masked, multicenter study. Patients were randomized to DEX implant (n = 123) or sham procedure (n = 120) and received 2 protocol-mandated intravitreal ranibizumab injections. The main outcome measure was injection-free interval to first as-needed ranibizumab injection. ***Results:*** DEX increased the injection-free interval versus sham (50th percentile, 34 vs. 29 days; 75th percentile, 85 vs. 56 days; p = 0.016). 8.3% of DEX versus 2.5% of sham-treated patients did not require rescue ranibizumab (p = 0.048). Visual acuity and retinal thickness outcomes were similar in DEX and sham-treated patients. Only reports of conjunctival hemorrhage (18.2 vs. 8.5%) and intraocular pressure elevation (13.2 vs. 4.2%) were significantly different in the DEX versus the sham treatment groups. ***Conclusion:*** DEX reduced the need for adjunctive ranibizumab treatment and showed acceptable tolerability in nvAMD patients.

Introduction

Neovascular age-related macular degeneration (nvAMD), a common cause of legal blindness in individuals over the age of 50 [1–4], is characterized by choroidal neovascularization (CNV) [5, 6]. CNV tissue consists of blood vessels, inflammatory cells, and mesenchymal cells within a loose extracellular matrix [7]. Subretinal leakage,

Members of the ERIE writing committee and ERIE study group investigators are listed in the appendix.

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hemorrhage, and fluid accumulation can lead to rapid vision loss, but nonvascular components of the disease process, such as inflammation and fibrosis, are also believed to contribute to disease progression [8–10]. Inflammatory involvement has been demonstrated in studies of excised CNV tissue of nvAMD patients. Growth of CNV into the subretinal pigment epithelium space may be augmented by activated macrophages and other inflammatory cells that secrete enzymes and cytokines that degrade Bruch's membrane [6].

Vascular endothelial growth factor (VEGF) stimulates angiogenesis and vascular leakage and is believed to have a primary role in CNV associated with nvAMD. Anti-VEGF agents are currently approved for first-line treatment of CNV in nvAMD: pegaptanib (Macugen®; Valeant Pharmaceuticals International Inc., Toronto, Ont., Canada), an aptamer to VEGF; ranibizumab (Lucentis®; Genentech Inc., South San Francisco, Calif., USA), a recombinant humanized Fab fragment of a murine monoclonal anti-VEGF antibody, and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, N.Y., USA), a recombinant fusion protein with binding domains from human VEGF receptors. However, outcomes are suboptimal for many patients.

A treatment approach that targets multiple components of the disease process may effectively prevent progression and restore vision in nvAMD [7, 8, 11–13]. One approach that has been used focuses on both angiogenesis and the underlying inflammatory factors. Although oral corticosteroids are potent anti-inflammatories, they are associated with severe systemic side effects [14]. Intravitreal injections of triamcinolone acetonide and dexamethasone have a more favorable safety profile and have been used off-label as adjunctive therapy to anti-VEGF agents and photodynamic therapy in the treatment of nvAMD [15–19]. Corticosteroids inhibit the capillary dilation, leukocyte migration, and edema associated with inflammation [20]. They may also block the fibroblast activation and proliferation that leads to scarring [21]. High-dose corticosteroid pulse dosing has been shown to cause apoptosis of cells involved in an inflammatory response, including peripheral T cells and eosinophils [22–24]. In animal models, intravitreal corticosteroid injections have been shown to inhibit both VEGF production [25] and CNV membrane development [26].

Dexamethasone is approximately 5 times more potent than triamcinolone [27] and has demonstrated less toxicity in cultures of human retinal pigment epithelium cells [28] and human lens epithelial cells [29]. As dexamethasone is cleared rapidly (half-life <4 h) from the vitreous humor after a single intravitreal injection [30–32], an intravitreal biodegradable drug delivery system (Novadur®; Allergan Inc., Irvine, Calif., USA) allows controlled release of dexamethasone over an extended period [33]. Dexamethasone intravitreal implant (DEX implant) 0.7 mg (Ozurdex®; Allergan) consists of a biodegradable copolymer, polylactic-*co*-glycolic acid, that contains micronized dexamethasone, which is slowly released. A single-use applicator system is used to place DEX implant in the vitreous through a 22-gauge needle [34]. Shown to be safe and effective in phase 2 and 3 trials [35, 36], DEX implant was recently approved for use in the treatment of diabetic macular edema. DEX implant 0.7 mg is also approved for the treatment of branch and central retinal vein occlusion [37–40], and for noninfectious uveitis that affects the posterior segment [41, for a review see Herrero-Vanrell et al. 42].

The purpose of this study was to evaluate the efficacy and safety of DEX implant 0.7 mg used as adjunctive therapy to ranibizumab in patients with CNV secondary to nvAMD. Our clinical hypothesis was that adjunctive therapy with DEX implant would decrease or delay the need for retreatment with ranibizumab.

Procedures

Study Design and Patients

This was a 6-month, randomized, multicenter, single-masked, parallel-group study in patients with CNV secondary to age-related macular degeneration. The protocol was conducted in accordance with applicable Good Clinical Practice regulations at 54 sites worldwide, and was approved by an institutional review board or independent ethics committee at each site. All patients provided informed consent prior to participation in the study. The study is registered with the trial identifier NCT00511706 at http://clinicaltrials.gov.

Eligibility for the study was evaluated at a screening visit. Key criteria are listed in table 1. If both eyes were eligible for the study, the eye with the worse best-corrected visual acuity (BCVA) was selected as the study eye. Two patient cohorts were enrolled: those with no prior treatment for nvAMD in the study eye (treatment-naïve cohort) and those with previous treatment for nvAMD (prior treatment cohort). Eyes previously treated with the following were excluded: foveal thermal laser or photodynamic treatment of nvAMD within 3 months prior to the screening visit; intraocular injection of an anti-VEGF treatment within 6 weeks prior to the screening visit; intravitreal or periocular corticosteroid treatment within 3 months prior to the screening visit; topical corticosteroid therapy within 4 weeks prior to the screening visit, or a history of intravitreal triamcinolone acetonide injection at doses >4 mg.

Intervention

At the completion of the screening visit (day –28), eligible patients were treated with ranibizumab 0.5 mg in the study eye. Four weeks later, at the baseline study visit (day 0), the need for retreat-

Table 1. Key eligibility criteria for study participation

Inclusion criteria	Exclusion criteria
Patients ≥50 years of age Subfoveal CNV secondary to nvAMD Required ranibizumab therapy for treatment of nvAMD *Study eyes* Total size of the lesion ≤12 Macular Photocoagulation Study disc areas (30.48 mm^2) Active CNV (classic or occult) representing ≥50% of the area of the lesion BCVA of ≥19 and ≤69 letters (approximately 20/40 and 20/400 on the Snellen scale) using the Early Treatment Diabetic Retinopathy Study method	*Patients* Glaucoma Diabetic retinopathy Active ocular infection at screening or the baseline visit History of an increased IOP in response to steroid treatment that was ≥10 mm Hg and reached a level of ≥25 mm Hg or that required treatment with laser, surgery, or >1 IOP-lowering medication *Study eyes* Subfoveal scarring, fibrosis, or atrophy Retinal pigment epithelium tear that included the fovea Presence of any causes of CNV other than nvAMD or any other ocular disease that could compromise vision Aphakia or presence of anterior chamber intraocular lens History of pars plana vitrectomy Current treatment with ≥2 IOP-lowering medications Screening or baseline IOP >23 mm Hg if untreated or >21 mm Hg if treated with 1 IOP-lowering medication

ment of the study eye was evaluated on optical coherence tomography (OCT) and clinical examination. Only patients who demonstrated at least 1 of the following criteria were eligible for retreatment with ranibizumab: macular cysts; subretinal fluid; pigment epithelial detachment (PED); a ≥50-μm increase in the central retinal subfield mean thickness from the lowest measurement at the previous visit, and new subretinal hemorrhage. Patients were also randomized at the baseline visit in a 1:1 allocation to adjunctive treatment with DEX implant 0.7 mg or sham procedure. Randomization was stratified by cohort, presence or absence of PED, and retinal angiomatous proliferation (RAP). Patients and personnel conducting the key outcome measure assessments including BCVA, OCT, fluorescein angiography (FA), and fundus photography (FP) were masked to treatment.

A single-use applicator with a 22-gauge needle was used to place DEX implant in the vitreous cavity through a self-sealing scleral oblique/biplanar injection [34]. For the sham procedure, an applicator without a needle or study medication was pressed against the conjunctiva and the actuator was depressed, with an associated audible click identical to the active treatment. At the next study visit (days 7–14), all randomized patients received a second protocol-mandated ranibizumab 0.5-mg injection. For patients who still met the study-defined retreatment criteria, up to 5 additional ranibizumab treatments were administered during outcome assessment visits at weeks 5, 9, 13, 17, and 21. At each visit, the investigator determined whether the patient qualified for retreatment with ranibizumab by satisfying at least 1 of the retreatment criteria. The final outcome assessment visit was at week 25.

Endpoints

The primary efficacy outcome measure was the ranibizumab injection-free interval, defined as the time from the second protocol-mandated ranibizumab injection (days 7–14 after randomization with either DEX or sham) to the determination of eligibility to receive the first as-needed ranibizumab injection. Key secondary efficacy measures included BCVA in both eyes at each visit, central retinal subfield thickness, and foveal center point thickness evaluated with OCT in the study eye at each visit, and the areas of CNV, leakage from CNV, and the total lesion evaluated with FA and FP in the study eye at screening and week 25. BCVA was measured with the Early Treatment Diabetic Retinopathy Study method. The OCT measurements of central retinal subfield and foveal center point thickness, FAs, and fundus photographs were independently analyzed by masked evaluators at a central reading center as well as by the investigator. Key safety measures included AEs, intraocular pressure (IOP), biomicroscopy, and ophthalmoscopy at each visit.

Sample Size

The sample size calculation was based on an estimated ranibizumab injection-free median interval of 60 days in the sham group (extrapolated from published data [43]) and 122 days in the DEX implant group (assuming a between-group difference of 2 months to be clinically meaningful). Given these estimates, the expected proportion of patients who would not be eligible to receive any retreatment of ranibizumab by day 180 was 36% in the DEX implant group and 12.5% in the sham group, with a corresponding hazard ratio of 0.492. With a sample size of 90 patients in each cohort (45 in each treatment group), a 0.05 level two-sided log rank test for equality of survival curves was estimated to provide 80% power to detect a difference of this magnitude in the ranibizumab injection-free interval. Anticipating a dropout rate of 10%, the planned study size was 100 patients in each cohort.

Statistical Analyses

The analyses of efficacy variables were based on the intent-to-treat patient population consisting of all randomized patients. Safety parameters were evaluated in the population of all random-

ized patients who received DEX implant or sham procedure. Separate analyses for each cohort were specified in the statistical analysis plan for the study.

The ranibizumab injection-free interval was calculated as the date of the determination of the eligibility for a third injection (the first as-needed injection) minus the date of the second (protocol-mandated) injection and was analyzed using the Kaplan-Meier method. In the analysis, observations for patients who were ineligible for a ranibizumab retreatment prior to week 25, or who discontinued the study prior to meeting the eligibility for a third injection, were censored at study exit. The null hypothesis of no difference between treatment groups in the cumulative probability of requiring ranibizumab retreatment was tested for the overall patient population and each cohort using a two-sided log-rank test with an alpha level of 0.05. In addition, the ranibizumab injection-free interval was analyzed using the Cox proportional hazards model with treatment and covariates of cohort, presence or absence of baseline PED, and RAP in the model. The between-group difference in the proportion of patients who required no additional injection of ranibizumab was compared using the Cochran-Mantel-Haenszel test with modified ridit scores stratified by cohort and baseline PED and RAP to control for the randomization stratification factors of baseline characteristics. In the stratified analysis, the treatment effect was examined separately within each stratum and then combined for an overall estimate across the strata. Categorical variables were analyzed using the Pearson χ^2, Fisher's exact, or Cochran-Mantel-Haenszel test. Continuous variables were analyzed using analysis of variance.

Results

A total of 310 patients were screened and received the first protocol-mandated ranibizumab injection. At the baseline study visit, 67 of these patients either failed to meet the retreatment criteria (n = 31) or were ineligible for the study due to other reasons (n = 36) such as lesion size, BCVA, or significant medical events. The remaining 243 patients were randomized and received DEX implant or sham, followed 1–2 weeks later by the second protocol-mandated ranibizumab injection (fig. 1).

There were no significant differences in baseline demographics, study eye characteristics, or ophthalmic history between the treatment groups in either cohort (table 2). However, in the treatment-naïve cohort, the mean lesion size of CNV by FA was significantly larger in the sham group than in the DEX implant group (7.17 vs. 5.20 mm^2, respectively; p = 0.046), and in the prior treatment cohort, the duration of CNV was significantly longer in the DEX implant group than in the sham group (26.6 vs. 19.6 months, respectively; p = 0.034). The most commonly used previous treatments for nvAMD in the prior treatment cohort were bevacizumab [65.6% (84/128) of patients; mean number of injections: 3.8] and ranibizumab [42.2% (54/128) of patients; mean number of injections: 4.0].

The overall study completion rate was 94.7%; rates were high in each treatment group and cohort. The most common reasons for early study discontinuation were entry criteria for study not met, lost to follow-up, and nonocular adverse events unrelated to treatment. None of the patients discontinued due to treatment-related adverse events.

The primary efficacy analysis found that in the overall patient population, the ranibizumab injection-free interval was statistically significantly greater in patients treated with DEX implant than in patients who received the sham procedure (p = 0.016; fig. 2). The 50th percentile (median) of injection-free survival was 34 days in the DEX implant group and 29 days in the sham group; the 75th percentile of injection-free interval was 85 days (12 weeks) in the DEX implant group and 56 days (8 weeks) in the sham group. In the non-PED subgroup, for DEX implant versus sham, the 50th percentile (median) of injection-free interval was 56 versus 34 days, and the 75th percentile was 91 versus 68 days, respectively. The difference in ranibizumab injection-free interval for the PED subpopulation was not significant (p = 0.405 for adjunctive therapy vs. ranibizumab alone).

The ranibizumab injection-free interval was also analyzed using the Cox proportional hazards model with treatment, PED, and RAP as covariates. Treatment and PED were significant predictors with a hazard ratio of 0.750 (95% CI 0.576, 0.977; p = 0.033) for the DEX implant group versus sham and 1.505 (95% CI 1.151, 1.968; p = 0.003) for patients with baseline PED versus otherwise. Thus, the hazard of requiring the as-needed ranibizumab injection for patients in the DEX implant group was only 75% of that for those of the sham group. The hazard for patients with baseline PED was 1.5 times more than that for patients without baseline PED. The estimated coefficients for baseline RAP and cohort were not statistically significant based on this model.

Among patients who received the 2 protocol-mandated injections of ranibizumab, the percentage of patients who did not require any as-needed injections was 8.3% (10/120) in the DEX implant group and 2.5% (3/118) in the sham group (p = 0.048). The mean number of as-needed ranibizumab injections over the course of the study was lower in patients treated with DEX implant than in those receiving the sham procedure (3.15 vs. 3.37, respectively). In both the treatment-naïve and prior treatment cohorts, as in the overall patient population, the cumulative probability of requiring a third (first as-needed)

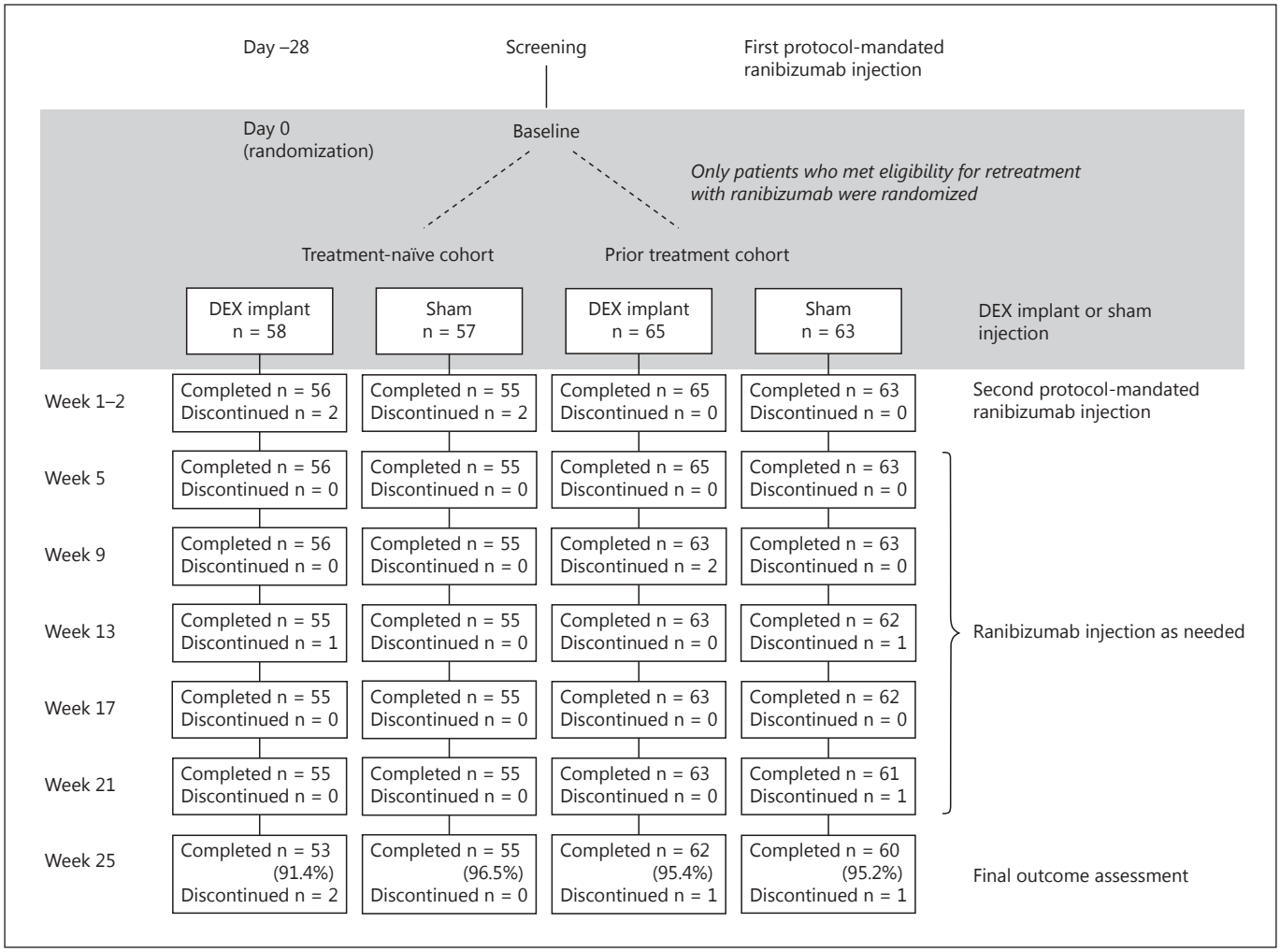


Fig. 1. Patient disposition. Reasons for early discontinuation from the study were nonocular adverse events unrelated to treatment in 3 patients (1 renal failure, 1 myocardial infarction, and 1 liver metastases, pneumonia, and myocardial infarction), 3 lost to follow-up, 2 for personal reasons, 1 for protocol violations, and 4 for failure to meet baseline study entry criteria.

ranibizumab injection over time was lower in patients treated with DEX implant than in patients receiving the sham procedure throughout the course of the study. However, the difference between treatment groups within each cohort was not statistically significant ($p = 0.133$ in the treatment-naïve cohort; $p = 0.066$ in the prior treatment cohort; fig. 2).

There were no statistically significant differences between treatment groups in the mean change from baseline BCVA in the study eye in the overall patient population (fig. 3). Mean changes from baseline BCVA in the study eye during follow-up ranged from +0.3 to +2.2 letters in the DEX implant group and from –0.4 to +2.4 letters in the group with sham procedure (table 3). In the treatment-naïve cohort, mean changes from baseline BCVA in the study eye ranged from +0.3 to +2.7 letters in the DEX implant group and from –0.5 to +2.6 letters in the sham group; none of the between-group differences were statistically significant. In the prior treatment cohort, mean changes from baseline BCVA in the study eye ranged from +0.4 to +2.4 letters in the DEX implant group and from –0.3 to +2.6 letters in the sham group; none of the between-group differences were statistically significant in either cohort. The distribution of changes from baseline BCVA in the study eye was similar between the treatment groups at week 25 in the overall patient population (fig. 4).

Table 2. Baseline demographics and clinical characteristics

	All patients		Treatment-naïve cohort (no prior nvAMD treatment)		Prior treatment cohort (prior nvAMD treatment)	
	DEX implant (n = 123)	sham (n = 120)	DEX implant (n = 58)	sham (n = 57)	DEX implant (n = 65)	sham (n = 63)
Age, years	76.1±8.8 (57–97)	76.2±8.5 (53–94)	77.4±9.5 (57–97)	77.4±7.1 (61–94)	74.9±8.1 (57–94)	75.0±9.5 (53–93)
Sex						
Male	47 (38.2)	51 (42.5)	21 (36.2)	22 (38.6)	26 (40.0)	29 (46.0)
Female	76 (61.8)	69 (57.5)	37 (63.8)	35 (61.4)	39 (60.0)	34 (54.0)
Race						
Caucasian	5 (4.3)	113 (94.2)	52 (89.7)	54 (94.7)	64 (98.5)	59 (93.7)
Asian	5 (4.1)	7 (5.8)	5 (8.6)	3 (5.3)	0	4 (6.3)
Hispanic	2 (1.6)	0 (0)	1 (1.7)	0	1 (1.5)	0
PED						
Yes	50 (40.7)	50 (41.7)	20 (34.5)	22 (38.6)	30 (46.2)	28 (44.4)
No	73 (59.3)	70 (58.3)	38 (65.5)	35 (61.4)	35 (53.8)	35 (55.6)
RAP						
Yes	4 (3.3)	4 (3.3)	4 (6.9)	3 (5.3)	0	1 (1.6)
No	119 (96.7)	116 (96.7)	54 (93.1)	54 (94.7)	65 (100)	62 (98.4)
Duration of CNV, months	16.4±20.4 (1–91)	12.3±16.2 (1–107)	4.9±10.3 (1–68)	4.1±14.0 (1–107)	26.6±21.7 (1–91)	19.6±14.5 (1–61)
Central retinal subfield thickness, μm	260.3±123.6	272.5±130.8	262.5±98.9	276.7±133.7	258.3±143.1	268.6±129.2
Foveal thickness, μm	218.0±77.2	222.4±77.3	217.3±63.9	225.4±74.5	218.7±87.7	219.8±80.5
Area of CNV, mm^2	9.8±7.7	9.2±6.8	5.2±4.6	7.17±5.39	9.34±7.56	7.82±7.21
Area of CNV leakage, mm^2	6.8±5.5	7.7±5.3	6.8±5.5	7.69±5.3	9.9±7.6	8.5±7.2
Area of total lesion, mm^2	9.8±7.7	9.2±6.8	7.3±5.5	9.0±5.96	11.9±8.8	9.4±7.6
BCVA, letters	55.5±15.3	58.1±12.6	55.4±15.5	56.5±13.3	55.5±15.2	59.5±11.9
IOP, mm Hg	14.6±3.0 (7–24)	15.2±2.9 (8–22)	14.5±3.0 (7–24)	15.2±2.8 (10–22)	14.8±3.0 (9–21)	15.2±3.1 (8–22)

Values are presented as mean ± SD (range) or n (%).

There were no statistically significant differences between treatment groups in the percentage of patients with at least a 15-letter improvement or worsening in BCVA in the study eye in either cohort at any study visit (table 3). At week 25, 14.8% (18/122) of patients treated with DEX implant and 15.8% (19/120) of patients who received the sham procedure had at least a 10-letter improvement in BCVA from baseline.

The between-group difference in the change from baseline foveal center point thickness in the overall patient population was statistically significant at the study visit for the second ranibizumab injection and at week 9, favoring the DEX implant group (fig. 5). There were no significant between-group differences in improvement in central retinal subfield thickness in the overall patient population during follow-up. However, sporadic statistically significant decreases in mean central retinal subfield thickness were seen in patients treated with DEX implant (28.8 μm at week 5 and 32.0 μm at week 9; $p \leq 0.004$). The areas of CNV, leakage from CNV, and the total lesion evaluated with FA in the overall patient population decreased significantly from screening to week 25 ($p \leq 0.002$) in both treatment groups with no statistically significant differences between groups (fig. 6).

Ocular adverse events in the study eye were reported for 49.6% (60/121) of patients treated with DEX implant and 41.5% (49/118) of those in the sham group ($p = 0.211$). None of these adverse events were serious. A higher incidence of conjunctival hemorrhage (18.2 vs. 8.5%; $p = 0.028$) and increased IOP (as determined by the investigator, 13.2 vs. 4.2%; $p = 0.014$) was reported in patients treated with DEX implant compared with the sham procedure. Cataract-related events were reported in 8 patients (6.6%) treated with DEX implant and 6 patients who received the sham procedure (5.1%; $p = 0.615$).

An IOP measurement of ≥25 mm Hg was observed at some point in the study for 18.2% (22/121) of the DEX implant group compared with 5.1% (6/118) of the sham group ($p = 0.002$), and most of these patients received IOP-lowering medications. Findings of IOP ≥25 mm Hg,

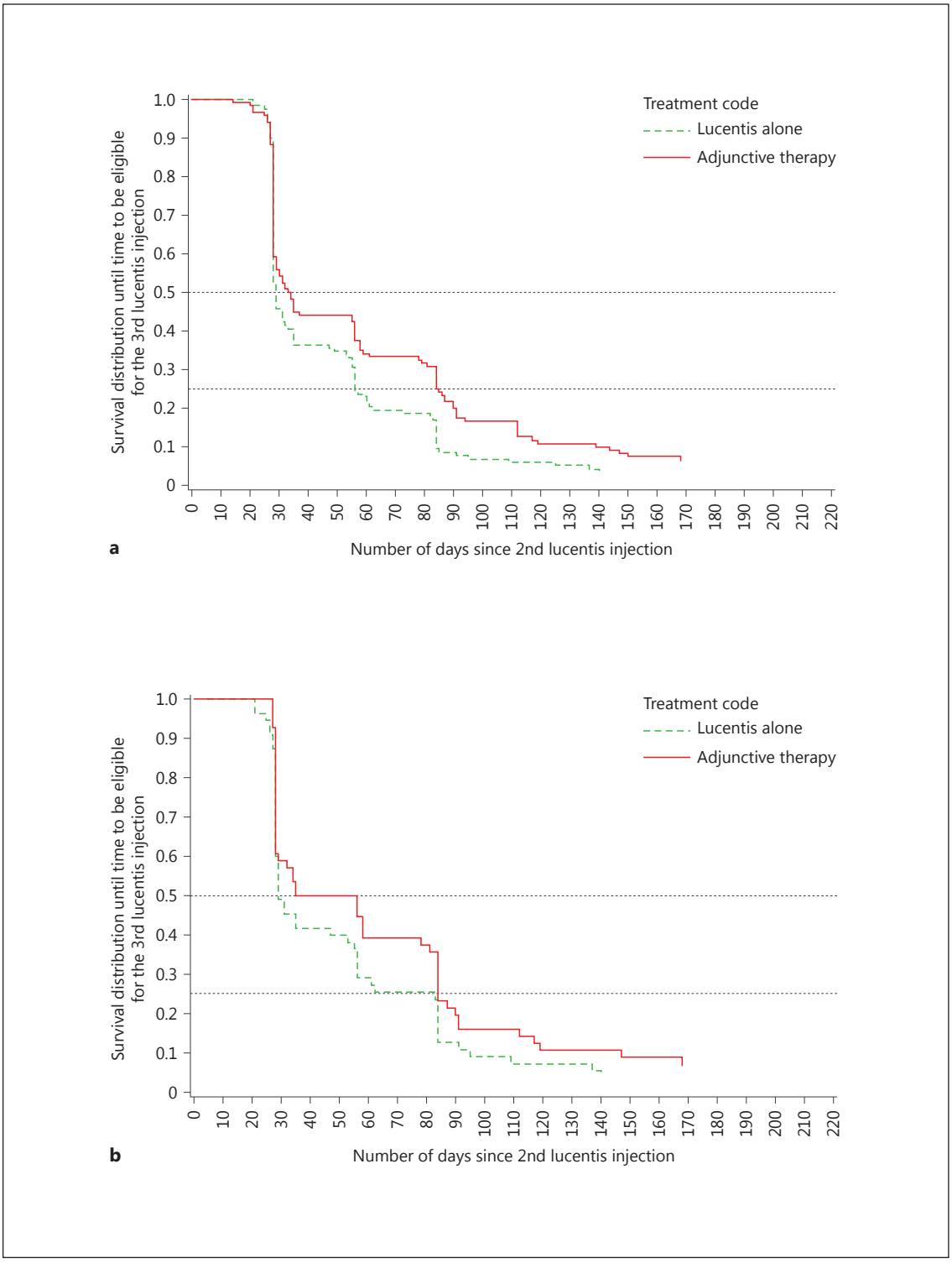
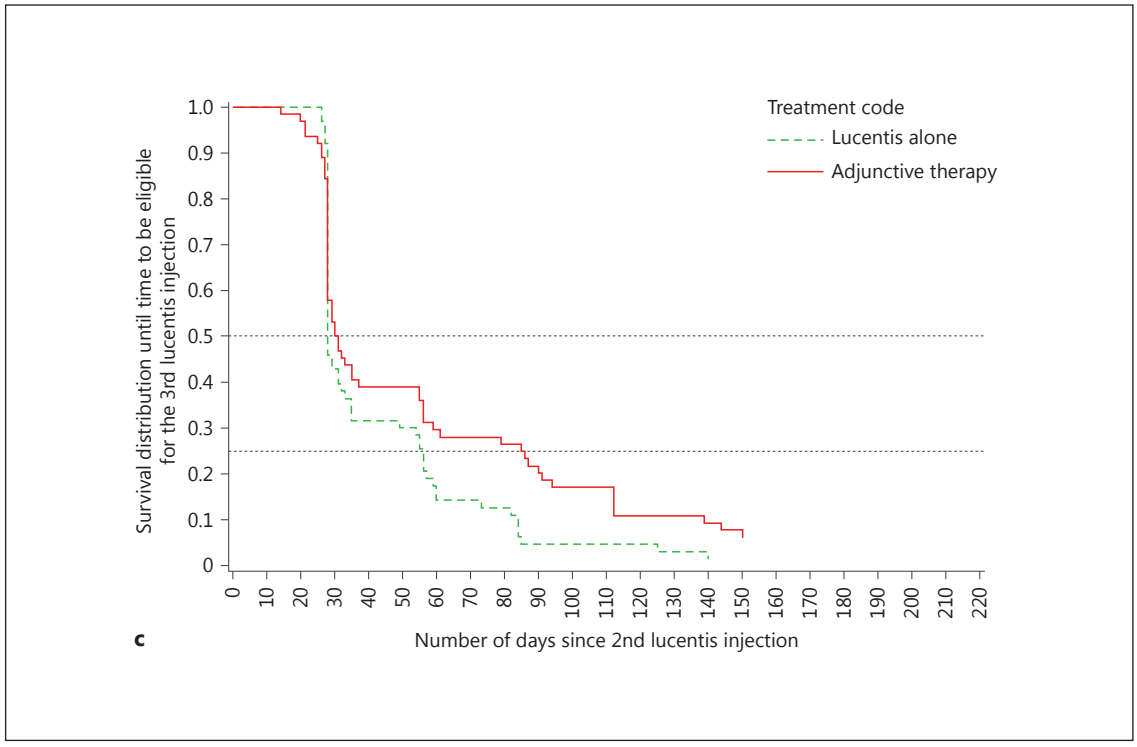


Fig. 2. Kaplan-Meier survival plot of the time from the second (protocol-mandated) dose of ranibizumab to the third (first as-needed) dose of ranibizumab in patients treated with adjunctive dexamethasone intravitreal implant or sham procedure. The cumulative probability of injection-free survival is shown for the overall patient population (**a**), the treatment-naïve cohort (patients with no prior treatment for age-related macular degeneration; **b**), and the prior-treatment cohort (patients previously treated for age-related macular degeneration; **c**). The between-group difference in injection-free survival in the overall study population was statistically significant (p = 0.016).

(For figure 2c see next page.)



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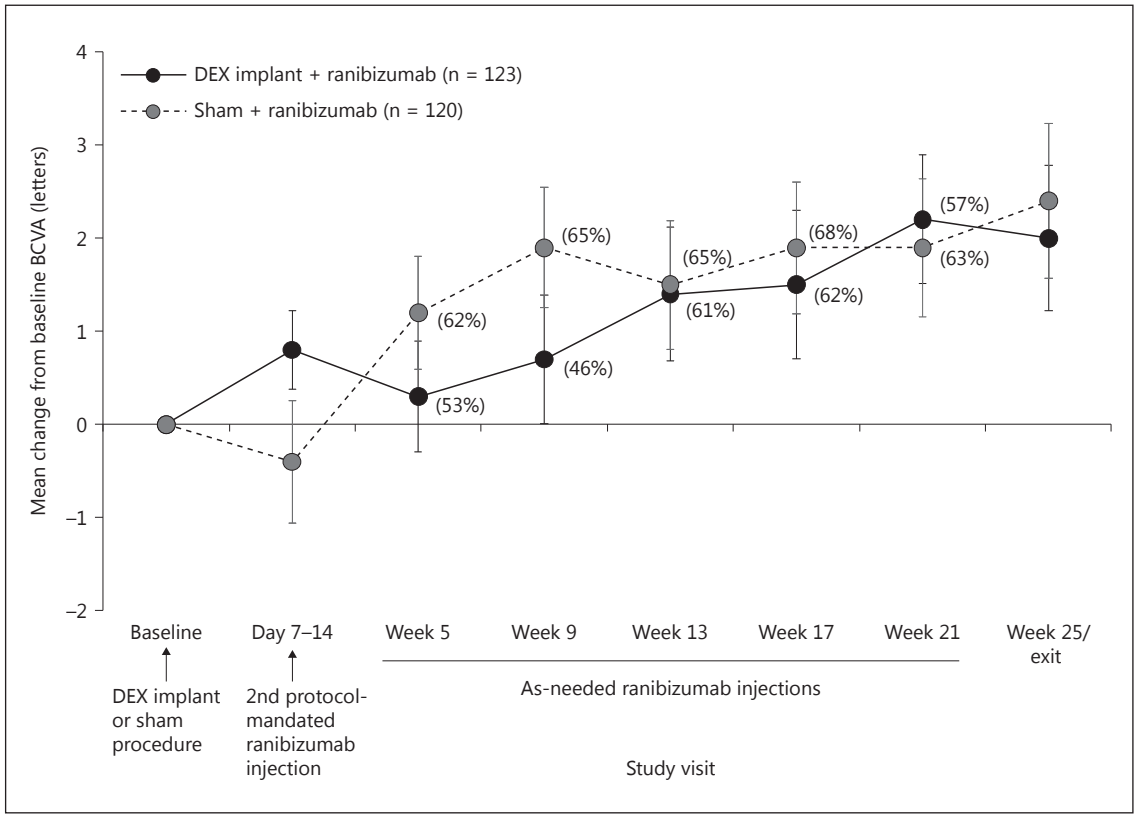

Fig. 3. Mean change from baseline BCVA in the study eye in the overall patient population. The percentage of patients treated with DEX implant or sham procedure who received an as-needed injection of ranibizumab at the study visit is shown in parentheses. Error bars show standard error of the mean.

Ophthalmologica 2015;234:40–54
DOI: 10.1159/000381865

Table 3. Efficacy outcome assessments

	All patients		Treatment-naïve cohort (no prior nvAMD treatment)		Prior treatment cohort (prior nvAMD treatment)	
	DEX implant (n = 123)	sham (n = 120)	DEX implant (n = 58)	sham (n = 57)	DEX implant (n = 65)	sham (n = 63)
Ranibizumab injections	4.8±1.8[a]	5.2±1.6[a]	4.4±1.7	4.9±1.7	5.2±1.8	5.5±1.5
Ranibizumab inter-injection variability[b]	110/123 18.8±16.8[a]	115/120 13.7±13.6[a]	51/58 20.6±16.3	53/57 15.6±14.5	59/65 17.3±17.2	62/63 12.1±12.5
BCVA (ETDRS) change from baseline to week 25, letters	122/123 2.0±8.6[a]	120/120 2.4±9.1[a]	58/58 1.5±10.6	57/57 2.6±8.4[a]	64/65 2.4±6.3[a]	63/63 2.3±9.9[a]
BCVA, ≥10-letter improvement (change from baseline to week 25), %[c]	18/122 (14.8)	19/120 (15.8)	11/58 (19.0)	9/57 (15.8)	7/64 (10.9)	10/63 (15.9)
BCVA, ≥15-letter improvement at week 25, %[c]	8/122 (6.6)	11/120 (9.2)	4/58 (6.9)	5/57 (8.8)	4/64 (6.3)	6/63 (9.5)
Central retinal subfield thickness, change from baseline to week 25, μm	105/123 –7.12±77.9	111/120 –13.0±97.7	52/58 –12.61±96.4	53/57 –34.70±106.6[a]	53/65 –1.74±54.4	58/63 6.84±84.9
Foveal thickness, change from baseline to week 25, μm	80/123 –6.2±59.0	77/120 –7.5±68.9	37/58 –11.2±62.8	39/57 –10.5±67.4	43/65 –2.0±56.0	38/63 –4.5±71.1
Total macular volume, change from baseline to week 25, μm	80/123 –0.12±0.46[a]	77/120 –0.18±0.44[a]	37/58 –0.23±0.48[a]	39/57 –0.26±0.51[a]	43/65 –0.02±0.43	38/63 –0.11±0.34[a]
Area of CNV leakage, change from screening to week 25, mm^2	95/123 –2.32±4.93[a]	99/120 –1.73±5.47[a]	47/58 –2.26±5.54[a]	48/57 –2.10±4.94[a]	48/65 –2.39±4.31[a]	51/63 –1.39±5.94
CNV lesion size, change from screening to week 25, mm^2	95/123 –1.81±4.11[a]	99/120 –1.47±4.31[a]	47/58 –1.27±4.18[a]	48/57 –1.82±4.71[a]	48/65 –2.34±4.01[a]	51/63 –1.14±3.92[a]
Area of total lesion, change from screening to week 25, mm^2	95/123 –1.48±4.63[a]	99/120 –1.60±4.77[a]	47/58 –1.58±5.67	48/57 –2.34±5.83[a]	48/65 –1.39±3.38[a]	51/63 –0.91±3.40
Area of classic CNV, change from screening to week 25, mm^2	95/123 –0.75±1.72[a]	99/120 –0.45±2.08[a]	47/58 –0.82±1.76[a]	48/57 –0.53±2.53	48/65 –0.68±1.69[a]	51/63 –0.37±1.57

Values are presented as n/N and mean ± SD, or n/N (%). ETDRS = Early Treatment Diabetic Retinopathy Study.
[a] $p \leq 0.05$. [b] Mean of all standard deviations of the injection intervals between each injection. [c] One patient in the prior treatment cohort who received DEX implant had no data at week 25.

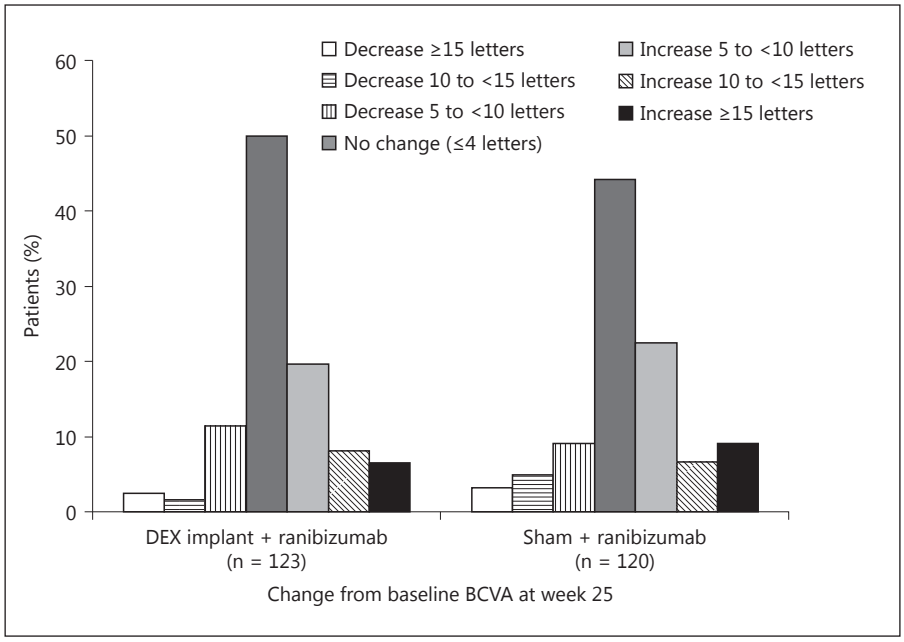

Fig. 4. Distribution of changes from baseline BCVA in the study eye in the overall patient population. There were no statistically significant differences between patients treated with DEX implant and sham procedure at any study visit. Results at week 25 (study exit) are shown.

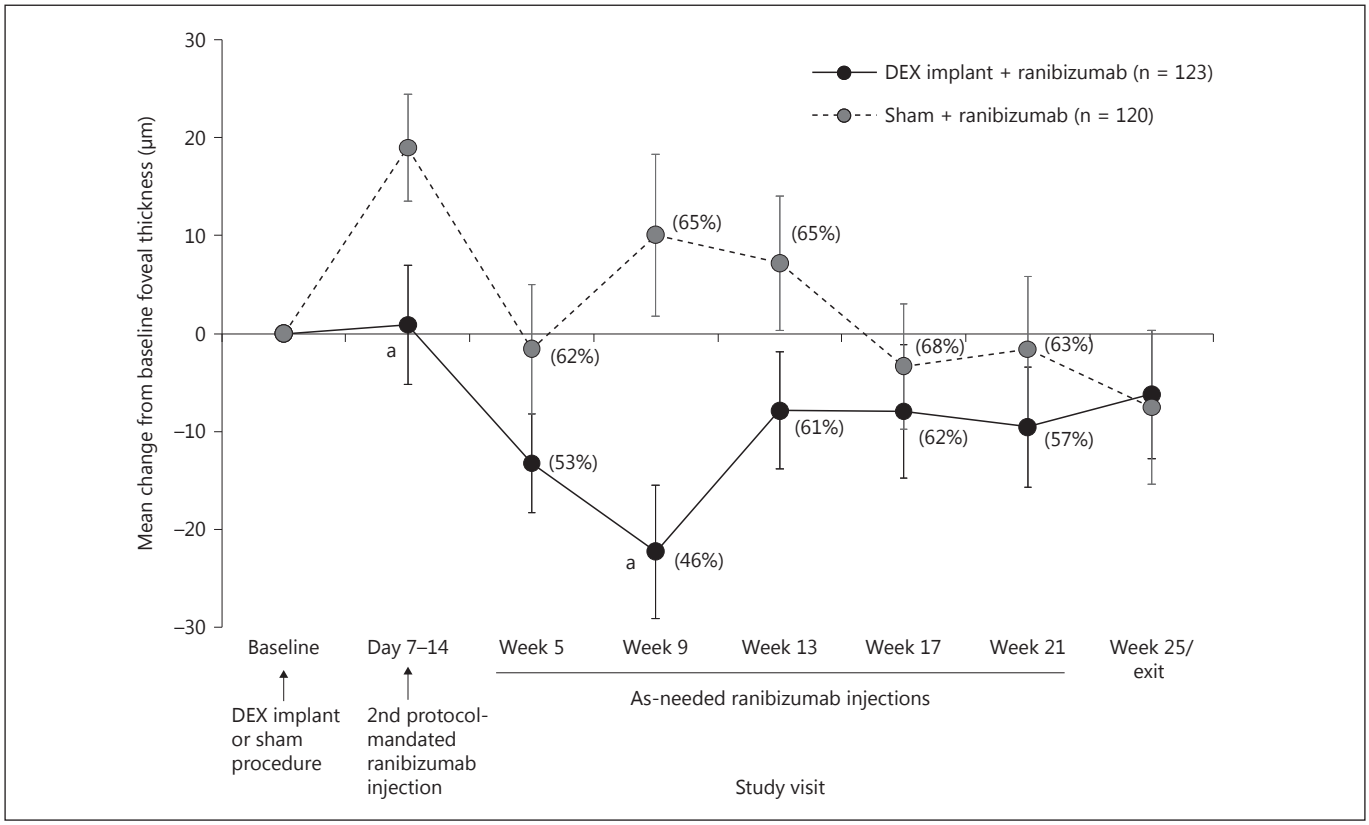

Fig. 5. Mean change from baseline center point foveal thickness in the study eye in the overall patient population. The percentage of patients treated with DEX implant or sham procedure who received an as-needed injection of ranibizumab at the study visit is shown in parentheses. Error bars show standard error of the mean. [a] $p \leq 0.027$ vs. sham.

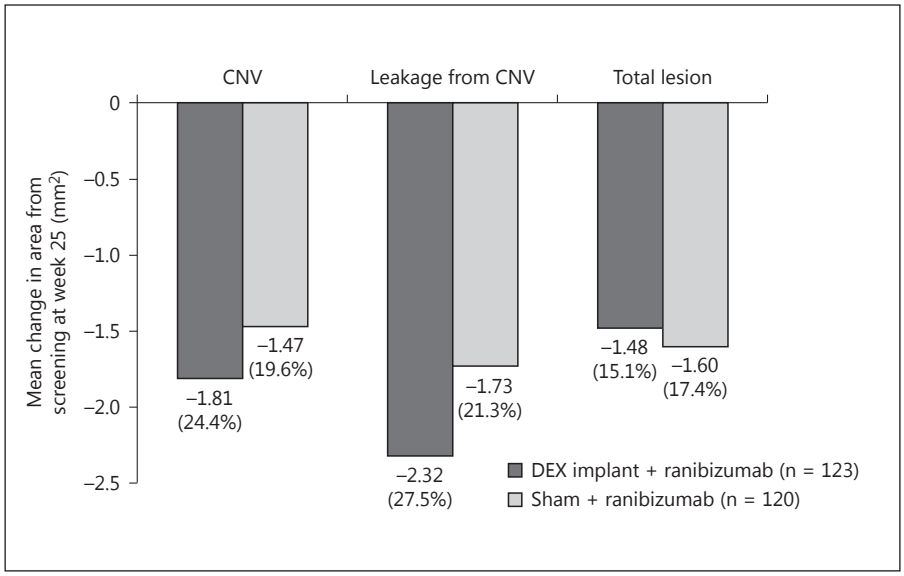

Fig. 6. Mean change in the area of the CNV lesion and leakage from CNV from screening to week 25 (study exit) in the study eye in the overall patient population. The area of CNV, leakage from CNV, and the total lesion decreased significantly ($p \leq 0.002$) in each treatment group with no statistically significant differences between groups. Mean areas at screening were 7.41 and 7.51 mm^2 for CNV, 8.44 and 8.12 mm^2 for leakage from CNV, and 9.78 and 9.20 mm^2 for total lesion in patients treated with DEX implant and sham procedure, respectively. There were no statistically significant differences between groups.

as well as findings of an increase in IOP from baseline of ≥10 mm Hg, peaked at week 9 in the DEX implant group (12.2% of patients for both findings). Only 1 patient (0.8%) had IOP >35 mm Hg at week 9. Among patients with no history of IOP medication use at baseline, 13.0% (15/115) in the DEX implant group, and 4.2% (5/118) in the sham group initiated IOP-lowering medication during the study. No surgeries were required to control IOP in any patients in the study. There were no statistically significant differences between treatment groups in the occurrence of IOP ≥25 mm Hg or increases in IOP from baseline of ≥10 mm Hg after week 9. At week 25, 1 patient (0.9%) in the DEX implant group and 2 patients (1.8%) in the sham group had IOP ≥25 mm Hg.

There were no significant differences between treatment groups in changes from baseline biomicroscopy and ophthalmoscopy findings in the study eye in the overall patient population, with the exception of conjunctival hemorrhage. Although reported in >2% of patients in each treatment group, the frequency of this finding was not statistically significantly different between groups.

Discussion

Although intravitreal anti-VEGF therapy is currently the most effective treatment for nvAMD, it is not effective in all patients, and frequent injections, usually monthly, are required to maintain its therapeutic benefit [44]. In the Comparison of Age-Related Macular Degeneration Treatments Trial at 1 year, 56% of patients who received ranibizumab monthly had fluid on OCT [45]. Inflammation represents another potential target of therapy in nvAMD, which could be approached with corticosteroids. Combination treatment using therapies with different mechanisms of action may allow a reduced frequency of intravitreal injections and improve long-term efficacy, safety, and outcomes [7, 8, 11–13]. In this study, adjunctive treatment with DEX implant significantly delayed the first as-needed injection of ranibizumab and significantly reduced the need for repeated ranibizumab treatment in patients with CNV secondary to nvAMD. The number of patients requiring no additional injections of ranibizumab was higher in the DEX implant group than in the sham group. Patients in the DEX implant group, however, had an additional scheduled intravitreal injection for implant placement, which in clinical practice can be reduced by performing both treatments on the same day. Visual outcomes and decreases in CNV size and leakage were as favorable in patients treated with adjunctive DEX implant as ranibizumab alone, despite the reduced frequency of ranibizumab injections. Statistically significant improvements in central retinal subfield thickness were seen only in patients treated with the combination therapy (DEX implant and ranibizumab). Additionally, there was a clear decrease in leakage area in the prior treatment group who received DEX.

Approximately 50% of patients in the treatment-naïve cohort and 60% of patients in the prior treatment cohort

for nvAMD required the first as-needed ranibizumab injection at week 5 (4 weeks after the second injection), regardless of whether they had received the DEX implant or the sham procedure. However, after week 5, the cumulative probability of requiring a third (first as-needed) ranibizumab injection over time was lower in patients treated with DEX implant than in patients receiving the sham procedure. Although the differences between treatment groups for the time to the first as-needed injection of ranibizumab within each cohort were not statistically significant, the difference between treatment groups is statistically significant in the overall patient population.

Patients in this study required retreatment after an initial ranibizumab injection due to continued edema, PED, or new subretinal hemorrhage. Thus, the study population consisted of patients who did not respond adequately to a single ranibizumab injection and may have included patients with loosely controlled VEGF that is difficult to treat even with multiple injections. Only one third of the patients in the study had gained at least 2 lines in BCVA from screening at the end of the study, after an average of 5 ranibizumab injections. The patients responded favorably to DEX implant; DEX implant treatment reduced central foveal thickness in the study population compared with the sham procedure. However, few patients demonstrated a sustained, clinically significant improvement in BCVA from baseline in either treatment group.

The injections of DEX implant were well tolerated. Increased IOP is a well-described side effect of intravitreal corticosteroid treatment [46, 47], and in this study an IOP ≥25 mm Hg occurred in 18.2% of patients treated with DEX implant. In all cases, the IOP was subsequently controlled with IOP-lowering eye drops; no laser or surgical intervention was required. The only other adverse event that was more common in the DEX implant group than in the sham group was conjunctival hemorrhage.

Intravitreal injections of anti-VEGF have generally been associated with fewer ocular complications than intravitreal corticosteroid injections. However, monthly treatment with ranibizumab may be associated with an increased risk of cerebrovascular incidents [48, 49]. Thus, the use of an adjunctive treatment (e.g. DEX implant) that would allow reduced frequency of ranibizumab injections may be associated with improved safety in large patient populations. As inflammatory cells associated with CNV tissue may induce CNV and stimulate other pathologic processes, such as fibrosis, that lead to vision loss in nvAMD [8–10], immunologic effects of high initial steroid concentrations following DEX implant administration, such as leukocyte apoptosis [22–24, 50], may account for the beneficial effect of DEX implant observed in this study.

A potential limitation of this study involves how investigators were masked. Although OCT, FA, and FP results were evaluated by masked readers at a central reading center, the investigators who determined study eligibility and the need for retreatment were not masked with respect to treatment assignment. Also, a single injection of DEX implant was given with a 6-month follow-up. Subsequent studies in patients with retinal vein occlusion indicate that DEX may be efficacious for approximately 3–4 months from implant [40, 51]. Taking into account that the mean duration of the effectiveness of DEX implant varies between 4 and 6 months, it would have been valuable to know whether the statistically significant increase in the time interval before the first as-needed injection was also prolonged over the following injections, but this was beyond the original scope of the study. Finally, the study sample size may have been too small as it was based on an estimated ranibizumab injection-free median interval of 122 days in the DEX implant group and 60 days in the sham group.

In summary, the results of this pilot proof-of-concept study demonstrate that DEX implant has the potential to influence the administration regimen of ranibizumab in nvAMD patients. Combination treatment with DEX implant and ranibizumab provided the same efficacy and allowed a statistically significant, though modest, reduction in the frequency of ranibizumab injections compared with ranibizumab used alone. DEX implant may also prove to be useful in combination with other treatments for nvAMD. Additional studies will be needed to further define the role of DEX implant and develop new algorithms for the treatment of neovascular ocular disease.

Conclusion

In a 6-month single-masked, randomized, sham-controlled study, patients with nvAMD received intravitreal ranibizumab 0.5 mg, followed 4 weeks later with DEX implant 0.7 mg or sham procedure. The implant modestly delayed and reduced the need for repeated ranibizumab treatment, and had an acceptable safety profile.

Appendix

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Disclosure Statement

This study was sponsored by Allergan Inc. (Irvine, Calif., USA). B.D. Kuppermann, R.K. Maturi, M. Goldstein, M. Singer, A. Tufail, and D. Weinberger have no proprietary interest in the study medications or Allergan Inc. B.D. Kuppermann is a consultant for Allergan Inc. X.-Y. Li, C.-C. Liu, J. Lou, and S.M. Whitcup are employees of Allergan Inc. and own stock in the company through matching benefits. Writing and editorial assistance was provided to the authors by Kate Ivins, PhD, and Lauren Swenarchuk, PhD, of Evidence Scientific Solutions, Philadelphia, Pa., USA, and funded by Allergan Inc. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

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